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(54) ANTHELMINTIC COMPOSITIONS AND USE

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1., a company incorporated in England do hereby declare the invention for which we pray that a Patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the control of nematode infections of domesticated animals.

Dogs and cats and other domesticated animals are prone to infections of ascarids and hookworms. Not only can the infections be severely debilitating, especially in young animals, but infections of the roundworm *Toxocara canis* represent a potential hazard to man as the cause of the visceral larva migrans syndrome.

Treatment of such infections has not previously been satisfactory: multiple doses have been needed or there has been insufficient control of infections of immature worms. Thus for example, control of immature ascarids infections in dogs using the most common of remedies, piperazine, provides only 84% clearance of ascarids at a dose of 400 mg/kg body weight, and this dose far exceeds the commonly recommended dose of 100 mg/kg.

The compound haloxon {*O,O* - di - (2 - chloroethyl) - *O* - (3 - chloro - 4 - methyl-coumarin - 7 - yl)phosphate} is an anthelmintic which has found considerable use in the control of nematode infections in ruminants, especially sheep, cattle and horses. The compound, bidimazium, in the form of its iodide and other salts, {2 - (*p* - dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl)thiazolium cation} has been reported to be active against hookworms in the dog.

It has now been found that bidimazium and haloxon, when administered together in the weight ratio of 1/2 respectively, to cats and dogs, provide excellent control of ascarids and hookworm infections. The combination can be used to provide a high degree of control of both mature and immature infections when administered orally as a single dose, and there is no antagonism of anthelmintic activity or potentiation of toxicity of the component compounds. The activity also manifests itself, contrary to the behaviour of bidimazium alone, to a similar extent when the host animal has an empty stomach as when it is on a milk or solid diet.

The haloxon/bidimazium combination may be used to control ascarids and hookworm infections especially in dogs and cats, and in particular infections of *Toxocara canis*, *T. cati*, *Toxascaris leonina*, *Ancyclostoma caninum*, *A. tubaeforme* and *Uncinaria stenocephala*.

Depending upon the nature of the worm burden and the size and age of the animal, dose ranges of 6 to 28 mg/kg of bidimazium and 12—56 mg/kg of haloxon may be used in the ratio of 1/2 by weight, respectively, to obtain control of infection. Animals should be dosed initially at 3 weeks of age, then at 6 and 12 weeks, and thereafter at intervals of 6 to 12 weeks to minimize or prevent resurgence of infection.

Bidimazium and haloxon are administered orally to the host animals, preferably as a single combined dose of the compounds formulated with pharmaceutically acceptable carriers to provide a pharmaceutical composition, or admixed with food additives. The carriers are preferably finely divided solids, but liquids may also be used, for example to provide suspensions of the active ingredients. Preferably both compounds are finely divided to a particle size weight median diameter of 5 to 50 μ prior to incorporation in a composition or administration to an animal. Capsules, and cachets containing the powdered components may be used, but tablets which are film- or sugar-coated and (if film-coated) are scored, are preferred. Convenient tablets contain 25 mg bidimazium with 50 mg haloxon; and 100 mg bidimazium with 200 mg haloxon.

It will be understood from the foregoing description that included within the scope of the present invention, but not limited thereto, are the following features which we will claim:—

(a) A pharmaceutical composition suitable

chloroethyl) - *O* - (3 - chloro - 4 - methylcoumarin - 7 - yl) phosphate and a pharmaceutically acceptable salt of the 2 - (*p* - dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium cation wherein the thiazolium salt (calculated as the cation) and the phosphate are administered in a weight ratio of 1 to 2 respectively.

10. A method according to claim 9 wherein the thiazolium salt is the iodide.

11. A method according to either of claims 9 and 10 wherein the thiazolium salt (calculated as the cation) and the phosphate are respectively administered in amounts in the ranges 6 to 28 and 12 to 56 mg per kilogram of animal bodyweight.

12. A method according to any of claims 9 to 11 wherein the animal is a dog or a cat.

13. An orally ingestible pharmaceutical composition substantially as hereinbefore described with particular reference to Example 2.

14. A method for treating ascarids and hookworm infections of a domesticated animal, substantially as hereinbefore described with particular reference to Example 1.

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